

HIFU for Bone Metastases and other Musculoskeletal Applications

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Abstract

Keywords

- High-intensity focused ultrasound
- bone metastases
- osteoid osteoma
- pain palliation
- interventional radiology

High-intensity focused ultrasound (HIFU) is a totally noninvasive procedure that has shown promising results in the management of numerous malignant and nonmalignant conditions. Under magnetic resonance or ultrasound guidance, high-intensity ultrasound waves are focused on a small, well-defined target region, inducing biologic tissue heating and coagulative necrosis, thus resulting in a precise and localized ablation. This treatment has shown both great safety and efficacy profiles, and may offer a multimodal approach to different diseases, providing pain palliation, potential local tumor control, and, in some cases, remineralization of trabecular bone. In musculoskeletal field, HIFU received FDA approval for treating bone metastasis, but its application has also been extended to other conditions, such as osteoid osteoma, desmoid tumor, low-flow vascular malformation, and facet joint osteoarthritis. This article illustrates the basic principles of HIFU and its main effects on biologic tissues with particular attention on bone, provides a step-by-step description of the HIFU procedure, and discusses the commonly treated conditions, in particular bone metastases.

Objectives: Upon completion of this article, the reader will be able to discuss the basic principles of HIFU and its main effects on biologic tissues and identify the main sequential steps of the procedure and its application for both malignant and benign conditions in the musculoskeletal field.

High-intensity focused ultrasound (HIFU) is an emerging noninvasive technique that has shown promising results for the management of malignant and nonmalignant conditions.^{1,2} HIFU application has been mainly evaluated for uterine fibroids and bone lesions such as osteoid osteoma and bone metastases;^{3–7} nevertheless, other fields of application include lesions, such as pancreas, liver, breast, pro-

tate carcinomas, and soft-tissue sarcomas, and also functional neurological disorders, such as essential tremor or Parkinson's disease.^{8–14}

Differently from other ablative procedures, such as cryoablation or radiofrequency, HIFU is completely noninvasive and does not need ionizing radiation exposure; for that reason, it can be easily repeated in case of recurrence. The treatment can be performed in an outpatient protocol.

The procedure is performed by an interventional radiologist, who has direct control over the areas to be ablated, while a dedicated software automatically determines the optimal treatment parameters.

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Basic Principles of High-Intensity Focused Ultrasound

Energy Generation

Focused ultrasound devices are composed by a generator and a transducer: the first item produces ultrasound energy, while the transducer focuses the energy produced by the generator onto a well defined target lesion. The transducer contains groups of elements that can be individually adjusted in amplitude and phase, allowing the steering of the focal target to different locations, without moving the patient.

High-Intensity Focused Ultrasound Biological Effect on Tissues

Acoustic energy of HIFU systems is generated by piezoelectric elements that convert electric signals into sound waves within a frequency range of 200 kHz to 4 MHz, with a peak compression pressure of up to 70 MPa and peak rarefaction pressure of up to 20 MPa; the acoustic intensity ranges between 100 and 10,000 W/cm². At these energy levels, focused ultrasound determines a temperature rise in biological tissues inside the treated region, leading to coagulative necrosis at a thermal threshold of 65 to 85°C, depending on the tissue absorption coefficient.¹⁵

Delivery of ultrasound waves is generally fractionated into several sequential sonications, to ensure an accurate control of the borders of treated target area and an optimal synergy with temperature monitoring: each sonication covers a focal volume of 0.2 to 5 mm³ and lasts only a few seconds, reducing potential obstacles on energy distribution due to blood flow. Therefore, large volumes require a greater number of sonication to obtain an homogeneous thermal damage for the entire region of interest.¹⁶

Cavitations represent another potential effect that focused ultrasound may determine on tissues: they consist of a non-thermal phenomenon due to microbubbles formation at high acoustic intensities. When the dimension of these microbubbles reaches a critical value, they may implode, producing micro-shock waves that can damage surrounding tissues. The use of cavitation is generally avoided in clinical practice, as they may determine unpredictable effects.

Imaging Guidance

HIFU treatment can be guided and monitored with ultrasound (ultrasound-guided focused ultrasound [USgFUS]) or magnetic resonance (MR) imaging (MR-guided focused ultrasound [MRgFUS]). Both these techniques have shown efficacy in localizing the region of interest and in receiving feedback from that region during and after treatment. In case of USgFUS, both diagnostic and therapeutic transducers are incorporated in the same device, while for MRgFUS the transducer is directly embedded in MRI imaging table.

USgFUS is more easily accessible and less expensive. However, the effectiveness of the ultrasound-guided procedure is operator and patient dependent, and the targeting can be sometimes difficult because of limited contrast between target region and the surrounding healthy tissues; moreover, the intraprocedural assessment of safety and

efficacy is generally limited, as no quantitative feedback from tissue temperature can be obtained.

On the other hand, even though MRgFUS is less available and relatively more expensive, it allows a more reliable target delineation thanks to a higher contrast resolution, and provides an accurate quantitative feedback from the treated region. Because of these important advantages, MR guidance is generally preferred to ultrasound, especially in the management of bone lesions such as metastasis.

MR monitoring is performed with high-field magnets (1.5T or 3T MR scanners) and is mainly based on *phase-difference fast spoiled gradient-echo* sequences, which allow the assessment of thermal dose distribution on tissues, providing a real-time quantitative thermometric map. Specifically, this system benefits from temperature accuracy of $\approx 1^\circ\text{C}$, spatial resolution of ≈ 1 mm, and temporal resolution of ≈ 3 seconds, and represents a reliable tool to ensure efficacy and safety of the procedure, proving the achievement of cytotoxic levels on target area and avoiding at the same time unintentional thermal damage on surrounding healthy tissues. The treatment can be modulated according to thermal feedback: ultrasound energy can be increased or decreased, if the temperature rise is insufficient or excessive, respectively.

In case of bone lesions treatment, MR thermometry cannot perform direct measurements of temperature in bone tissue (because of the lack of mobile protons in cortical bone). In addition, temperature measurements in the bone marrow are not reliable, as proton resonance frequency thermometry cannot be applied on fat tissue. Nevertheless, the signal received from the surrounding soft tissues enables a precise evaluation of target area and protection of the surrounding regions.

High-Intensity Focused Ultrasound on Bone

Within the HIFU treatment domain, bone cortex represents a peculiar structure, characterized by a high ultrasound absorption rate. When the acoustic beam intersects bone surface, only a small portion of waves penetrates and reaches deeper locations, while the major part is absorbed and reflected to neighboring structures.¹⁷ For that reason, HIFU treatments were at first limited to superficial bone lesion, and deep locations were considered as nonfeasible targets. Following studies demonstrated that reflected ultrasound waves determined critical thermal damage to the adjacent periosteum (the most innervated structure of mature bone) and played a fundamental role in pain palliation;¹⁸ in fact, current treatments of bone lesions take advantage of this high absorption rate, by positioning the focal spot deep to the bone cortex, allowing the ablation of a larger bone surface area with the use of the near field of ultrasound beam. The peculiar absorption properties of bone also represent a further increase in the already high HIFU safety profile, as lower ultrasound energy levels are needed to achieve heating and ablation. Moreover, the introduction of innovative protocols with more flexible parameters allowed a more consistent portion of acoustic waves to penetrate deeper within the bone;¹⁹ particularly, the increase of energy levels, the increase of the duration of each sonication, and the decrease

of wave frequency are potential modulators that can facilitate penetration inside cortical bone, even though they may simultaneously increase the risk of bone fractures and damage to surrounding structures.

In case of cortical bone interruption, the ultrasound beam can be delivered following standard protocols with low risk of significant reflection, and may potentially obtain local tumor control.

Sonications are considered completely therapeutic beyond a threshold of 65°C, for both periosteum and target areas.

High-Intensity Focused Ultrasound Procedure

Imaging Evaluation

Preliminary imaging plays an essential role in treatment planning, in particular for the establishment of the optimal acoustic window and ultrasound beam conformation. Lesion margins must be correctly identified and included into target volume, while air, nontarget bone, and other reflecting structures have to be avoided by the energy path. Key parameters in this phase are target lesion size, location, and extent; its accessibility to ultrasound beam; and the presence of any highly absorbing or reflecting structure along the planned trajectory.

An optimal treatment planning requires an accurate evaluation on both CT and MR.

Unenhanced CT is essential, as it allows the characterization between osteoblastic and osteolytic metastases and the assessment of the integrity or infiltration of adjacent cortical bone.

On the other hand, MRI provides a great delineation of the metastases and its characteristics in terms of cellular density, vascularization, etc. These parameters are fundamental for the evaluation of treatment outcomes at follow-up.

Anesthetic

The type of anesthesia is chosen according to the type of procedure to be performed, the condition of the patient, and the level and type of pain that the patient expects to experience during and after the procedure. General anes-

thetic is usually reserved for procedures targeting upper trunk lesions (proximal humerus, scapula, sternum, and clavicle); on the contrary, lesions involving the limbs can be managed through ultrasound-guided peripheral nerve block and lesions located in the lower trunk, spine, or proximal femur, through spinal block.

Planning Phase

Planning phase is conducted just before MRgFUS treatment, with the patient already on the MR table.

- *Patient positioning* is the fundamental starting point, as it allows to place target lesion directly over the HIFU transducer, achieving the optimal acoustic window, the shorter length of beam path, and the lowest number of obstacles. MR acquisition is obtained afterward to confirm the optimal positioning (►Fig. 1).
- After that, with *calibration* step, the operator chooses the most appropriate position and orientation of HIFU transducer.
- In *loading* step, MR images are acquired as the base for subsequent planning strategy.
- In *segmentation* step, the operator defines the region of treatment, the skin surface, the bone cortex, and the areas surrounding the target lesion, with particular attention on those sensitive structures close to target region that may determine energy dispersion and unwanted thermal damage (*limited energy density regions*): these critical areas must be carefully identified and highlighted to avoid treatment-related side effects. On MR imaging, the operator also establishes fiducial anatomic markers in this phase, to detect and compensate physiologic or accidental motion of the patient during the treatment. In segmentation step, the treatment volume may be limited to the superficial periosteum for palliative denervation or it can involve also the deeper tumor tissue, to attempt a complete ablation of the lesion.
- In *planning* step, the dedicated software automatically establishes the optimal treatment plan calculating the sonication locations, the number of sonications, the

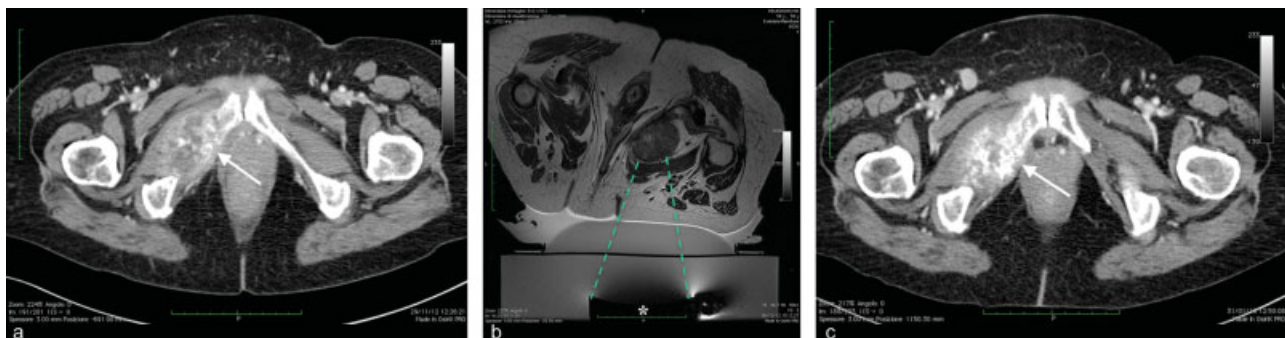


Fig. 1 (a) Preintervention CT scan of a 58-year-old woman with metastases on the right ischiopubic ramus (arrow), from a primitive tumor on the left kidney; the lesion shows a predominant osteolytic pattern and determines a complete alteration of bony structure. This patient suffered from severe pain condition (VAS score = 9). (b) Preliminary MRI scan showing patient positioning at the beginning of HIFU session; target lesion is placed directly over the transducer (asterisk), which is housed within the MRI table, achieving the optimal acoustic window and the shorter length of beam path, with the lowest number of obstacles (planned beam path is illustrated in dashed lines). (c) Three-month follow-up CT scan shows the persistence of bone metastases, which starts developing a sclerotic appearance (arrow); this patient referred a conspicuous pain relief (VAS score = 1).

energy levels, the sonication duration, the cooling duration, or the spot sizes. Each of these parameters can be modified by the operator at any moment.

- In *verification* step, a low-energy sonication test, below ablation threshold, is performed to confirm the beam path into the target area.

High-Intensity Focused Ultrasound Treatment

Once all the preliminary steps are correctly fulfilled, the actual treatment with full-energy sonications can start. As previously described, intact cortical bone usually requires lower energy levels (1,500–3,000 J) to obtain periosteal damage. In case of cortical erosion, the treatment can involve both adjacent vital periosteum and the soft-tissue component of the tumor: the latter generally requires higher energy levels (2,500–6,500 J). In this setting, a complete lesion control with ablation can be attempted in addition to pain palliation. During the procedure, real-time MR thermometry assesses the actual distribution of energy in the region of interest and the surrounding tissues, ensuring high safety and efficacy profiles.

Postintervention Management

After the procedure, patient management is generally based on the anesthetic approach: patients under local anesthetics or a spinal block are followed up in an outpatient setting, while patients receiving general anesthesia need 24-hour hospitalization. In the postprocedural phase, it is important to evaluate skin surface to identify treatment-related burns, to monitor vital signs, and to administrate pain relief drug if necessary.

Minor treatment-related side effects include pain in treated area, first-/second-degree skin burns less than 2 cm in diameter, or bruising in the treated area and transient fever; these conditions generally resolve within 2 weeks after the procedure. Major side effects include necrosis of nontarget tissue caused by heat conduction from bone cortex, hollow viscera perforation, skin burns with ulceration, and anesthetics-related complications (cardiac, pulmonary complications, drug reactions); these conditions may require medical treatment, may have sequelae, and their time of resolution is not defined. In case of bone lesion treatment, in addition to general procedure-related side effects, necrosis of surrounding soft tissues secondary to heat conduction from the cortex, loss of nearby joint function, and bone damage or necrosis with fractures may occur.

Postintervention Evaluation

Postinterventional evaluation is based on both clinical assessment and imaging studies to determine pain relief and tumor control, respectively.

Clinical evaluation mainly consists of pain measurements through visual analog scale (VAS), changes in drug usage schedule and quality of life assessment. All these parameters are periodically recorded along a period of at least 1 month after the procedure, and then compared with baseline preprocedural values to obtain a complete view of the trend in clinical outcomes. VAS is a 0 to 10 numeric pain scale, with 0 representing the complete absence of pain and

10 representing the worst possible pain. Clinical benefit is considered complete if a 0 VAS score is obtained without any increase in drug usage. A partial clinical response is defined by a drop of at least 2 VAS points from baseline conditions, with no increase in pain drug usage, or a reduction of 25% in drug usage without an increase in VAS score. Even though many questionnaires are available for quality of life assessment, the most used in painful metastasis normally is the Brief Pain Inventory Quality of Life questionnaire, which evaluates how pain can impact on some key features of daily living, such as physical activity, work, mood, ambulation, and sleep.

As previously described, imaging monitoring is routinely performed throughout each MRgFUS procedure thanks to sequential MR thermometric acquisitions. Nevertheless, imaging follow-up is also performed with periodic intervals after treatment, to evaluate lesion control. According to the protocol in our institution, imaging follow-up is performed immediately after the end of MRgFUS, at 1, 3, 6, and 12 months. Just after treatment, MRI with dynamic contrast-enhanced T1-weighted sequences is used to estimate the nonperfused volume (NPV) of target lesion; NPV is defined as the ratio between the post-treatment NPV and the whole pretreatment target volume. A complete overlap of the NPV with the original perfused lesion volume (NPV = 100%) is considered as a complete ablation of both the lesion and the periosteum. If target lesion was not completely accessible to ultrasound, the NPV should at least cover the periosteal surface to achieve pain relief rather than tumor control. At 1, 3, 6, and 12 months after treatment, both MRI and CT are used. CT is useful in identifying re-mineralization in treated areas as a further indicator of treatment success, while MR is repeated with dynamic contrast-enhanced T1-weighted sequences to assess the evolution of treatment effects in the target area and to evaluate potential tumor necrosis or recurrence (► Fig. 2).

High-Intensity Focused Ultrasound for Bone Metastases

When considering bone metastases, there are multiple mechanisms that can explain the effects of HIFU in terms of pain relief, including periosteum denervation, tumor debulking (with reduction in the pain related to the expansion of the mass), and the reduction of chemical mediators' release and the degree of osteoclast-mediated osteolysis.²⁰

MRgFUS has received U.S. Food and Drug Administration approval for pain palliation in patients with bone metastases. Pain treatment is reported to be effective in 60 to 100% of patients. The relief occurs rapidly and is durable, occurring within 3 days and lasting more than 3 months.

In 2013, a phase III randomized, placebo-controlled, multicenter trial of MRgFUS was performed with 147 patients: 64% of patients reported pain reduction at 3 months, with 20% of them obtaining complete pain relief; two-thirds of the patients achieved clinical response within 3 days. The most common complication was pain during the treatment; major complications (see later) occurred in 3% of the patients.²¹

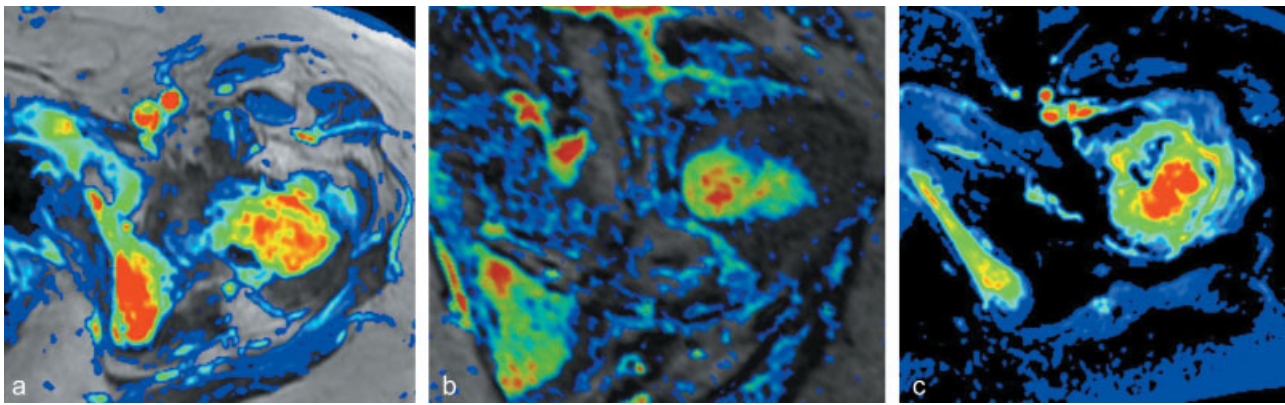


Fig. 2 (a) Preprocedural dynamic contrast-enhanced MRI showing highly vascularized bone metastasis on left ischiopubic ramus and left femoral neck of a 57-year-old man with colon carcinoma; the colorimetric map obtained from perfusion sequences clearly shows the lesions in yellow and red. (b) Immediately after treatment, MRI control shows a significant reduction in lesion vascularity, demonstrating an effective local tumor control. This patient reported a significant reduction of symptoms as well (from a baseline VAS score of 8 to a postoperative value of 2, starting from the following day). (c) However, at 6 months, MRI follow-up shows an increase in vascularization intensity and extent (particularly on the femur), which indicates disease progression; despite this condition, this patient continued to benefit from pain relief (VAS score of 2).

Currently, MRgFUS is recommended as a second-line treatment for pain palliation of nonspinal and non-skull bone metastases, after unsuccessful radiation therapy. It can be used as a first-line treatment when radiation therapy is contraindicated or the patient refuses to receive it. The main treatment goal is pain palliation, although tumor control can be attempted as a secondary goal in a small subset of patients, which includes patients who have breast or prostate cancer with a life expectancy of longer than 12 months and patients with oligometastatic disease.

The use of MRgFUS is generally limited to patients with known history of bone metastatic disease, if confirmed at imaging.¹⁸ There are no limitations based on the type of bone lesion (osteolytic or osteoblastic) or on the number of sessions a patient can undergo in cases of pain recurrence. In addition, there is no limit related to previous radiation therapy or chemotherapy, and the procedure can be performed without interrupting any concurrent chemotherapy.

Treatable lesions always need to be identified at imaging, and should be localized on nonarticular regions of extremities, ribs, sternum, pelvis, shoulders, and posterior regions of dorsal, lumbar, and sacral vertebrae. Further inclusion criteria, assessed on preprocedural planning phase, require that lesions should be at least 10-mm deep below skin surface, and that ultrasound beam path always has to reach the target lesion without encountering other structures with high absorption or reflecting properties, such as nontarget bone, air-filled organs, wide scars, or metallic implants/devices, as they shield the propagation of ultrasound and obscure targets beyond them.

Generally, patients excluded from the procedure present with contraindications to MRI, gadolinium or anesthetic; in case of high risk of fracture on the affected bone, or affected bone already treated with metallic tools, treatment cannot be performed, too. Moreover, nontreatable locations include the skull, vertebral bodies, superficial lesions (>1 cm below skin surface), or lesions close to nerve bundles (<1 cm).

High-Intensity Focused Ultrasound for Other Musculoskeletal Diseases

In addition to bone metastases, HIFU treatment has been extended to other benign musculoskeletal conditions.

Osteoid Osteoma

Currently, the standard treatment options for osteoid osteoma consist of medications, surgery, or minimally invasive techniques, with CT-guided radiofrequency ablation as the standard of care.²² MRgFUS offers important advantages, such as totally noninvasiveness, real-time temperature monitoring, and the possibility to repeat treatment with no concerns for radiation exposure, particularly important considering the typically young age of the patients.^{23,24} The mechanisms behind MRgFUS palliation are hypothesized to be the ablation of highly innervated periosteum and nidus vasculature, presumably interrupting the production of inflammatory prostaglandins and prostacyclins from the tumor.²⁵ Furthermore, a study described the occurrence of a progressive “restructuring” of the bone, with disappearance of any sign of the lesion at 12 to 24 months.²² In our experience, HIFU showed to be a safe, effective, and durable treatment option: 45 subjects with a median 8 VAS score underwent MRgFUS, and 87% of them reached and maintained a 0 VAS score at 3-year follow-up, with a consequent significant increase in terms of quality of life, without any procedure-related adverse event (→ Fig. 3).⁶ For that reason, HIFU has the potential to be part of a routine strategy for treatment of osteoid osteoma, replacing more invasive options.

Desmoid Tumors

Current standard treatments for desmoid tumors present significant limitations and morbidity, including poor efficacy of chemotherapy and its associated side effects: a 50% recurrence rate after surgery, even with negative margins, and a 5% risk of developing secondary malignancy after radiation.²⁶ According to preliminary evaluations, HIFU has

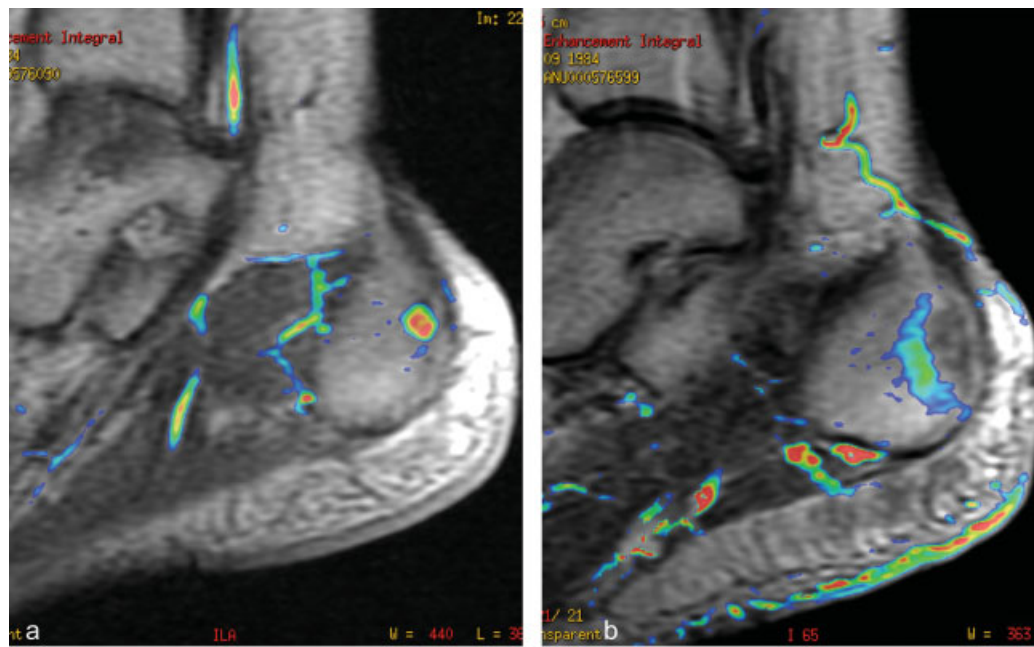


Fig. 3 (a) Preprocedural dynamic contrast-enhanced MRI showing an osteoid osteoma on the calcaneus of a 21-year-old woman suffering from considerable pain (VAS = 8) and limitations to walking and other daily activities; the nidus is clearly identified as a highly vascularized focus (red) in the color map. (b) Dynamic contrast-enhanced MRI scan obtained immediately after treatment shows a complete suppression of nidus vascularity as expression of local tumor control; only a mild and vague local increase of vascularity can be seen in the surrounding region, as a normal result of postprocedural inflammation, which spontaneously resolved within days. This patient reported an immediate clinical benefit as well (VAS = 2 on the very first day after treatment, which turned to 0 at 1 week and remained stable during our 3-year follow-up period).

shown promising results;²⁷ this technique can be particularly useful, as it can be repeated in case of recurrence and has not been associated with tumor spread, which can occur along the surgical incision if the tumor has not been completely removed. The first aim of HIFU for desmoid tumors is to cure or, if the mass is in close proximity to sensitive structures, to palliate; pain relief has been reported even with partial ablation of the tumor.²⁸ Further studies are needed to confirm these preliminary findings and to establish more tailored treatment parameters.

Vascular Malformations

Surgery or sclerotherapy are universally accepted as first-line treatment options for vascular malformations;²⁹ MRgFUS is being investigated as a possible alternative for painful low flow vascular malformations that have an unfavorable vascular anatomy for sclerotherapy or cannot be visualized adequately on ultrasound to allow guidance for sclerotherapy. The possible mechanism of MRgFUS is vessel vasoconstriction due to thermal and mechanical damage that eliminates the heat sink effect of blood, followed by coagulative necrosis after effective sonications.^{30,31} Preliminary studies highlighted an effective pain relief starting immediately after treatment, without reporting any side effect; however, future studies are needed to assess the long-term durability, and to establish tailored technical parameters, especially considering the vascular nature of these anomalies and the consequent possibility of heat dissipation.

Facet Joint Osteoarthritis

Current treatment options for facet joint osteoarthritis include oral medications, anesthetic and steroid intra-articular injections, radiofrequency neurolysis, and, in most severe cases, facet rhizotomy.³² Oral medications alone may not be effective and are typically associated with other therapies; intra-articular injections can be effective at providing temporary pain relief, and treatments should be periodically repeated; and radiofrequency ablation has shown a wide variability in effectiveness. An observational phase I pilot study demonstrated that HIFU determined an improvement in pain scores and functional disability, with results that are comparable to radiofrequency denervation;³³ however, a prospective randomized controlled trial comparing HIFU to control is needed to confirm these preliminary results.

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